

### REMARKS

Applicant respectfully requests reconsideration. Claims 32-47 were previously pending in this application. Claims 48-53 were previously withdrawn. Claim 32 is amended herein. Support for the amended claim is found throughout the application as filed, including for example at page 4, line 2; page 5, lines 16-17; and page 6 lines 10-15. No claims are canceled. No new claims are added. As a result, claims 32-47 are pending for examination with claim 32 being an independent claim. No new matter has been added.

### Rejection Under 35 U.S.C. 112

Claims 32-47 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method as claimed, wherein the vector comprises a gene encoding a hepatitis B virus surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in a vertebrate animal, does not reasonably provide enablement for the use of a vector encoding any other HBV antigen, including core antigens.

Without conceding the correctness of the Examiner's rejection, but rather in the interest of expediting prosecution, Applicant has amended the claims to recite that the vector is capable of expressing a hepatitis B virus surface or core antigen, or a fragment thereof. Thus, the scope of HBV antigen is no longer as broad as the Examiner indicates.

Applicant respectfully disagrees with the Examiner's position that the claimed methods are not enabled for HBV core antigens, because the art teaches that core antigens are capable of inducing a protective immune response. In support, Applicant provides herein evidence and arguments showing that (i) intramuscular injection with a plasmid encoding viral core antigens, in a model system that is predictive of immune response in humans, induces a protective response to subsequent virus exposure; (ii) wild-type HBV core antigens isolated from humans induce an adaptive immune response; and (iii) chimpanzees immunized with HBV core antigens are protective from further HBV challenge.

*WHV model is predictive of human HBV infection*

In response to Applicant's submission of the teachings of Lu M et al., (Lu M. et al., Journal of Virology, Jan. 1999, p. 281-289), as enabling support for the use of HBV core antigens in the claimed methods, the Examiner argues that woodchuck hepatitis virus (WHV) is distinct from HBV, with distinct surface and core antigens, and thus is not representative of immune response that may be raised using plasmids that encode HBV antigens. The Examiner concludes that WHV experiments would not provide sufficient guidance for raising a protective immune response with plasmids encoding HBV core antigens.

The Examiner's position is inconsistent with the view in the art that chronic WHV infection in woodchucks is an established model for HBV infection in humans. As articulated in Menne et al., "chronic WHV carrier woodchucks provide a well-characterized mammalian model for preclinical evaluation of the safety and efficacy of . . . *experimental therapeutic vaccines* . . . for the treatment and prevention of HBV disease . . .". (Menne S and Cote PJ; World J. Gastroenterol. 2007 January 7; 13(1):104-124.) Menne S, et al. further note that "the results of drug efficacy and toxicity studies in the chronic carrier woodchucks *are predictive* for responses of patients chronically infection with HBV." Thus, the skilled artisan would be expected to derive sufficient guidance for raising a protective immune response with plasmids encoding HBV core antigens based on the teachings of Lu et al that intramuscular injection with a plasmid encoding WHV core antigens controls subsequent WHV infection in woodchucks. (See, Lu M et al., e.g., Table 2 and Figure 7).

*Wild-type HBV core antigens obtained from human patients produce a humoral and cellular response*

Applicant previously submitted that the teachings of Lee Y.-S. et al., demonstrate that intramuscular injection of mice with an expression plasmid vector encoding Hepatitis B core antigens obtained from chronic active hepatitis patients results in a strong, specific antibody (Table 1) and cytotoxic lymphocyte (Figures 6 and 7) response. (Lee, Y.-S., et al., Immunology Letters 78 (2001) 13-20.)

The Examiner essentially dismisses these results arguing that the antigens were mutant forms of HBV core antigen and not disclosed in the instant specification. However, Lee Y.-S. et al.,

quite clearly teach that the Hepatitis B core antigens that induce the specific antibody and cytotoxic lymphocyte response are *wild-type* antigens. For example, Lee Y.-S. et al. state “our results suggest that HBc *wild-type* DNA-based vaccination strongly induced humoral and cellular immunity to HBV. . .”. (Lee, Y.-S., et al., at page 20, column 1.) The “mutations” that the Examiner refers are simply amino acids differences between wild-type core antigens identified by Lee Y-S et al., and core antigens disclosed in a different study. (Lee, Y.-S., et al., at page 16, column 1.) The skilled artisan will appreciate that HBV antigen sequences can differ among different HBV wild-type variants (See, e.g., Jazayeri M, et al., *J Viral Hepat.* 2004 Nov;11(6):488-501.)

The Examiner further argues that the immune responses in Lee Y.-S. et al. do not correlate with a protective effect. However, Lee Y.-S. et al. demonstrate a cytotoxic lymphocyte (CTL) response to core antigens, and the presence of CTLs that specifically recognize core antigens represents an adaptive immune response to the core antigen. (Id.) In HBV, such CTLs are associated with viral clearance, a protective effect (Id.; See, also, Ferrari C et al., *J Immunol.* 1990 Nov 15;145(10):3442-9.). Moreover, by inducing a helper T-cell response, HBV core antigen supports the development of protective anti-HBs antibodies (see Milich et al., *Nature.* 1987 Oct 8-14;329(6139):547-9).

*HBV core antigens are capable of inducing a protective immune response in primates*

Chimpanzees that have been immunized with hepatitis B core antigen<sup>1</sup> develop Hepatitis B core antibodies and exhibit protective effects against subsequent viral challenge with known infectious HBV. (Iwarson, S. et al., *Gastroenterology* 1985, 88:763-7; Tabor et al. US Patent 4,547,367 filed on Dec. 20, 1983; See also Murray K, et al., *Journal of Medical Virology* 23:101-107, 1987, commenting that the protective immune response induced by HBV core antigens in chimpanzees “supports the argument for trials in humans of a vaccine against HBV based upon or containing HBcAg . . .”. (Id.) While Iwarson et al. and Murray et al. do not teach administration of core antigen according to the claimed methods, the references support the proposition that exposure to HBV core antigen in primates results in a protective immune response to viral challenge.

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<sup>1</sup> (with adjuvant Figure 1 and without adjuvant Figure 2 of Iwarson, et al., 1985)

Based upon the foregoing, Applicant respectfully submits that the claimed invention was enabled as of the filing date of the application for the full scope of HBV antigens, including core antigens. Accordingly, withdrawal of the rejection of claims 32-47 under 35 U.S.C. § 112 is respectfully requested.

*HBV surface antigens*

The Examiner acknowledges that the claimed methods are enabled for use with HBV surface antigens. Since claims 39-40 and 44-47 specifically recite surface antigens, Applicant submits that any rejection in view thereof should be withdrawn.

**Double Patenting**

Claims 32-47 have been rejected on the ground of nonstatutory obviousness-type double patent as being unpatentable over Claims 1-14 of U.S. Patent No. 6,635,624. Applicants may file a Terminal Disclaimer depending on the claims that are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

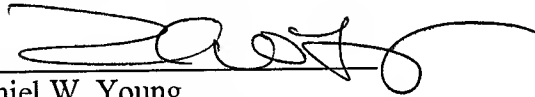
**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. O0277.70001US00.

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Respectfully submitted,

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